# The Increased Risk of Melanoma from Sildenafil & Tadalafil

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# Overview:

I. Qualifications

II. Summary of Opinions

III. Scientific Methodology

IV. Assessment of Causation

# Summary of Opinions

- **Task**
  - I was asked to review the literature to provide an impartial investigation of whether or not there is an epidemiologic association between sildenafil and tadalafil use and melanoma.
  - Once I determined an association exists, I was asked to conduct a causal assessment of the relationship between PDE5 inhibitor use and incident melanoma.
  - Provide a written report.

# Summary of Opinions

- **Available scientific research on sildenafil and tadalafil demonstrates a causative relationship between their use and the development of melanoma skin cancer.**

1. **Laboratory-based research demonstrates that mechanistically there is *biological plausibility***

2. **Population-based epidemiologic evidence demonstrates consistent positive associations between use of sildenafil and tadalafil and melanoma**

3. **An assessment of Bradford Hill criteria demonstrates associations are causal**

- "It is my opinion, to a reasonable degree of medical and scientific certainty, and based on my education, training, and experience, as well as my review of literature, that the use of PDE5-Is (sildenafil and tadalafil) increase the risk of development of melanoma in a vulnerable subset of patients."
  - Ahmed SDN, TDL Rpts. at 3. (JX13 & JX14)

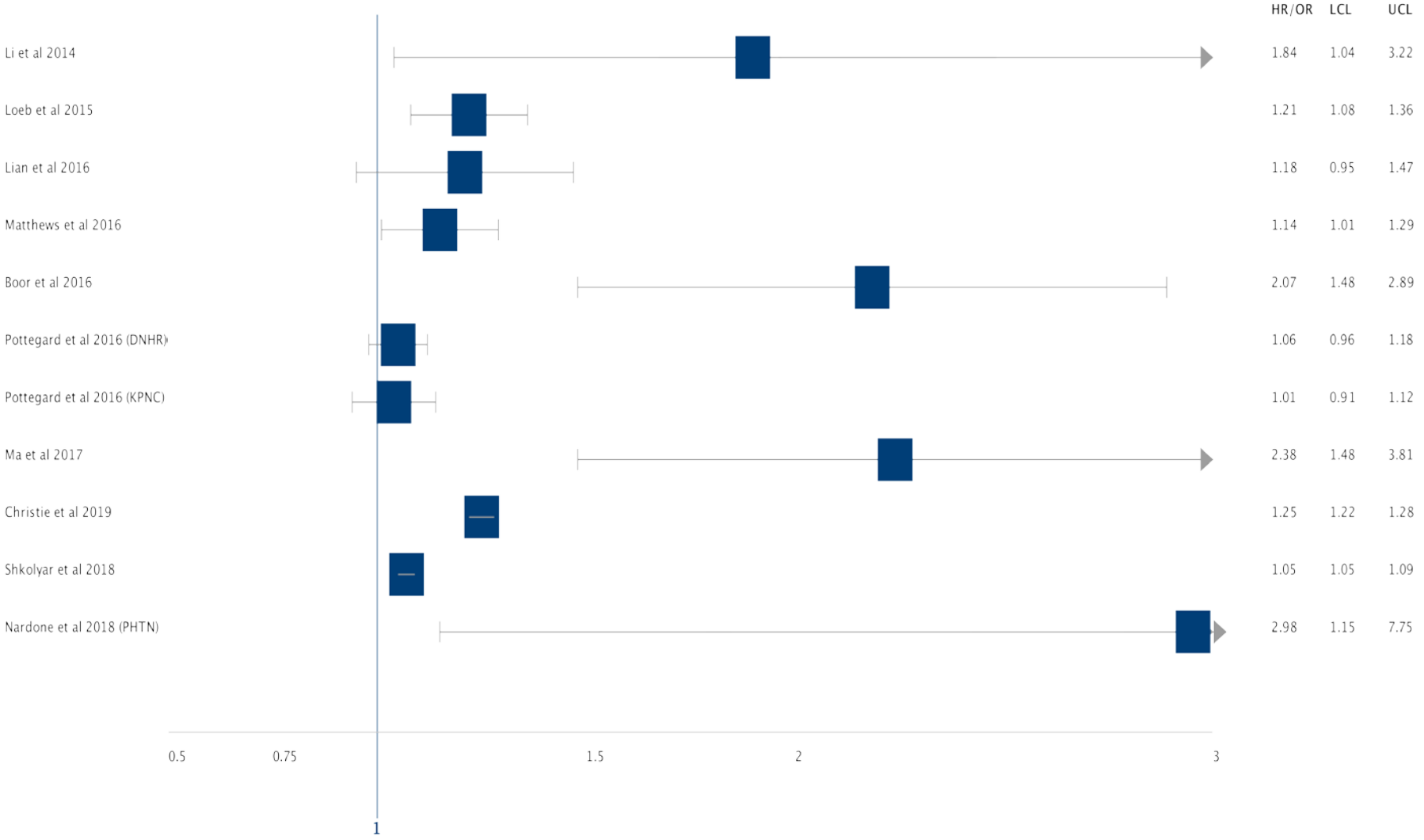
# Scientific Methodology

- **Reviewed published literature**
  - Epidemiologic literature
  - Laboratory-based literature
- **Conducted Bradford-Hill Causal Assessment**

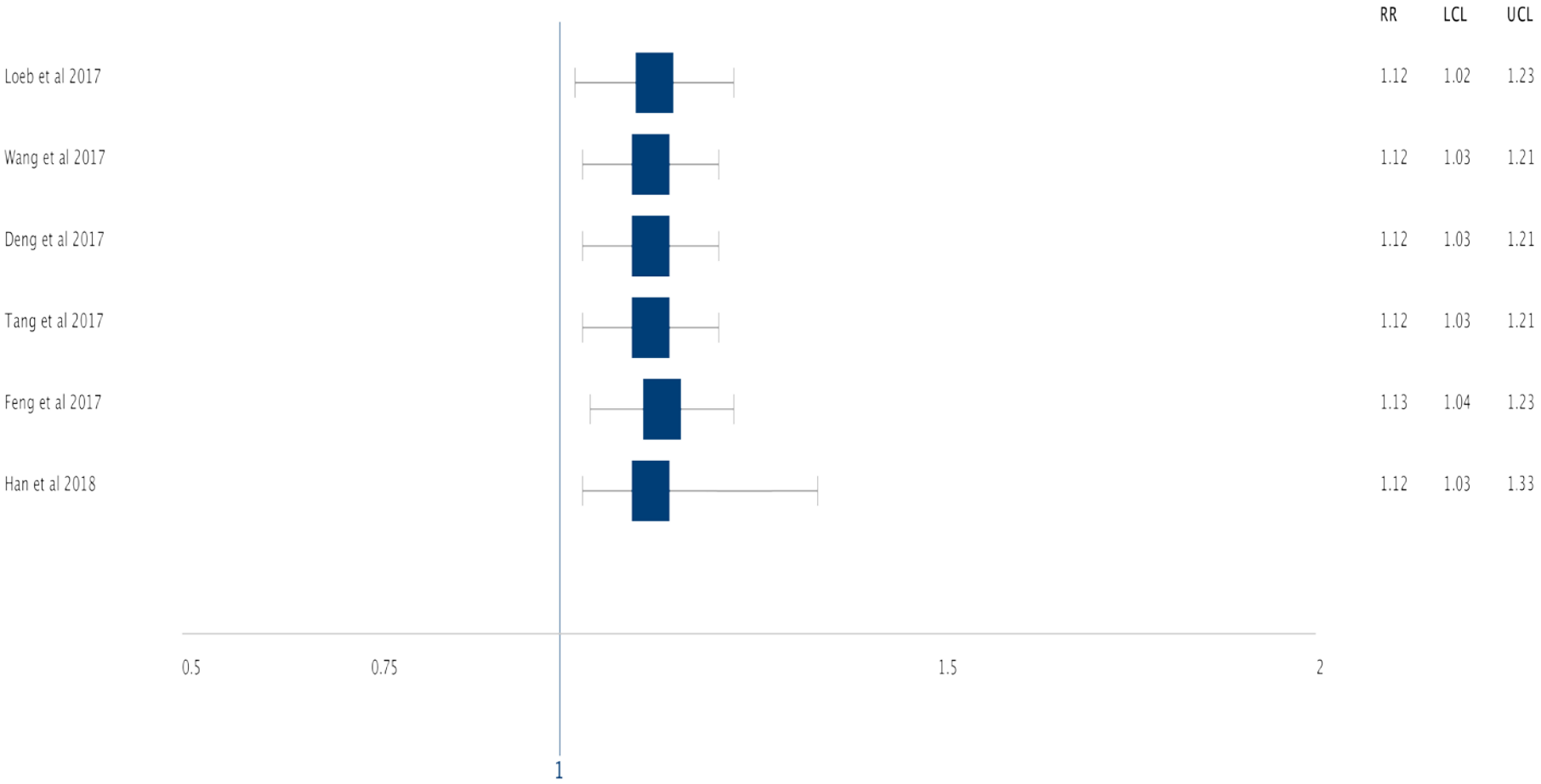
# Laboratory-Based Data

- **Considered biological plausibility**
  - Analyzed laboratory-based data
- **Conclusions**
  - Mechanistically there is biological plausibility that inhibition of PDE5, through administration of sildenafil or tadalafil, increases the risk of melanoma
- **Compared to Drs. Haq, Ganesan**
  - Independent of and consistent

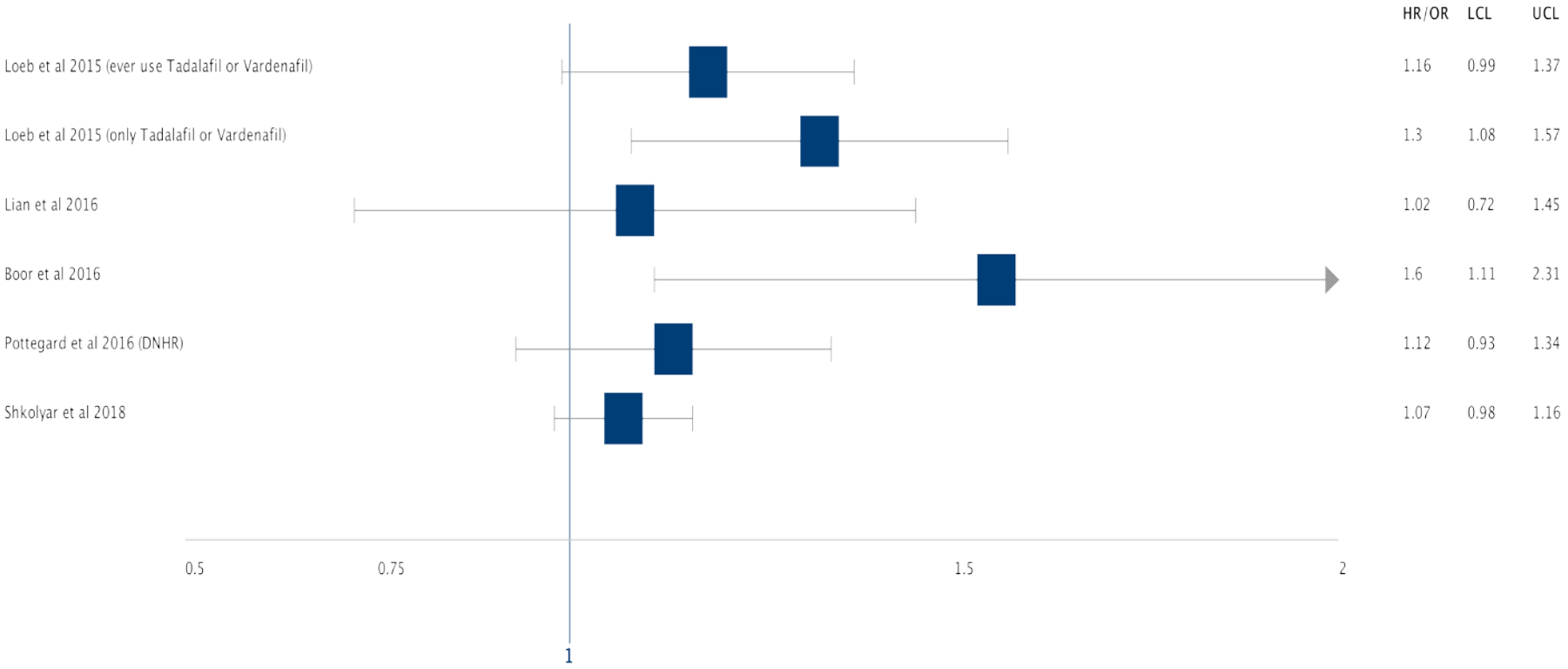
# Associations Between PDE5-I Use and Melanoma in Patients



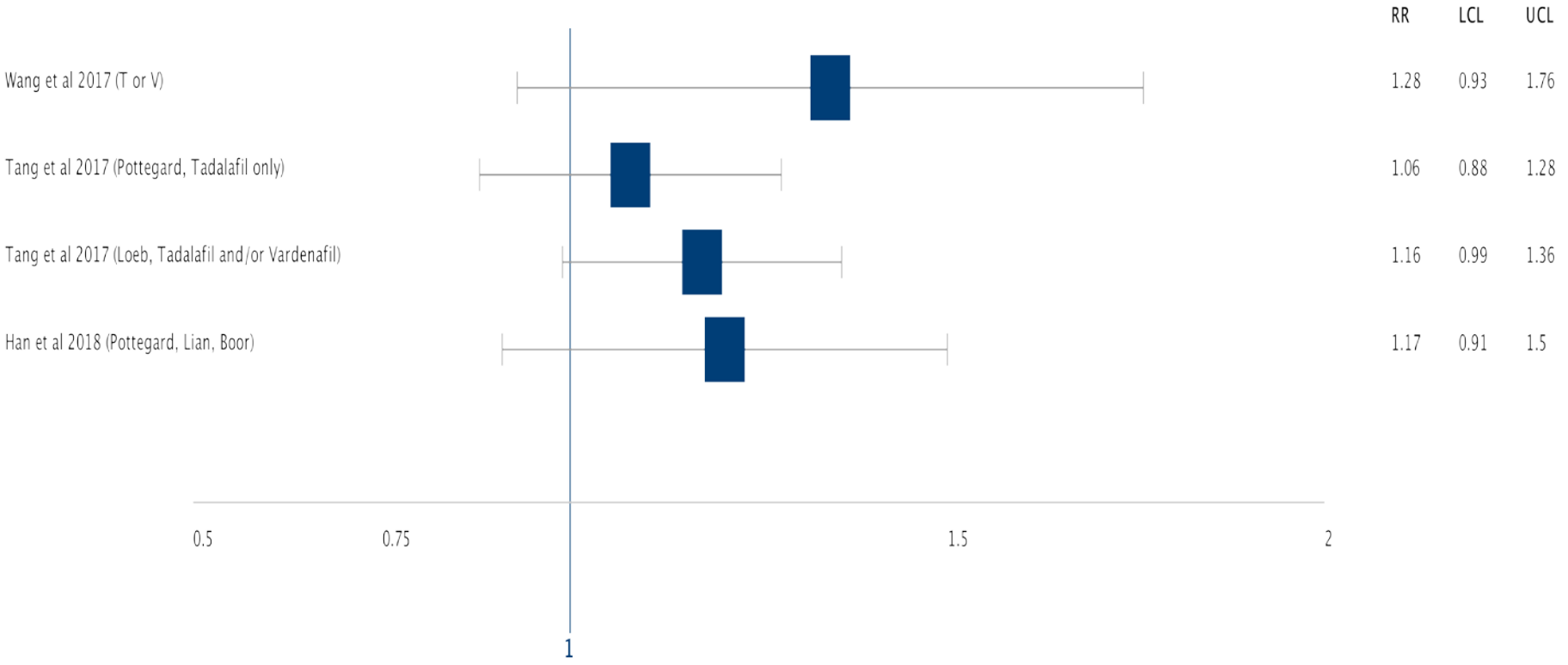
# Meta-Analyses: PDE5-I and Melanoma, Primary Outcomes



# Associations Between Tadalafil Use and Melanoma



# Meta-Analyses: Tadalafil and Melanoma



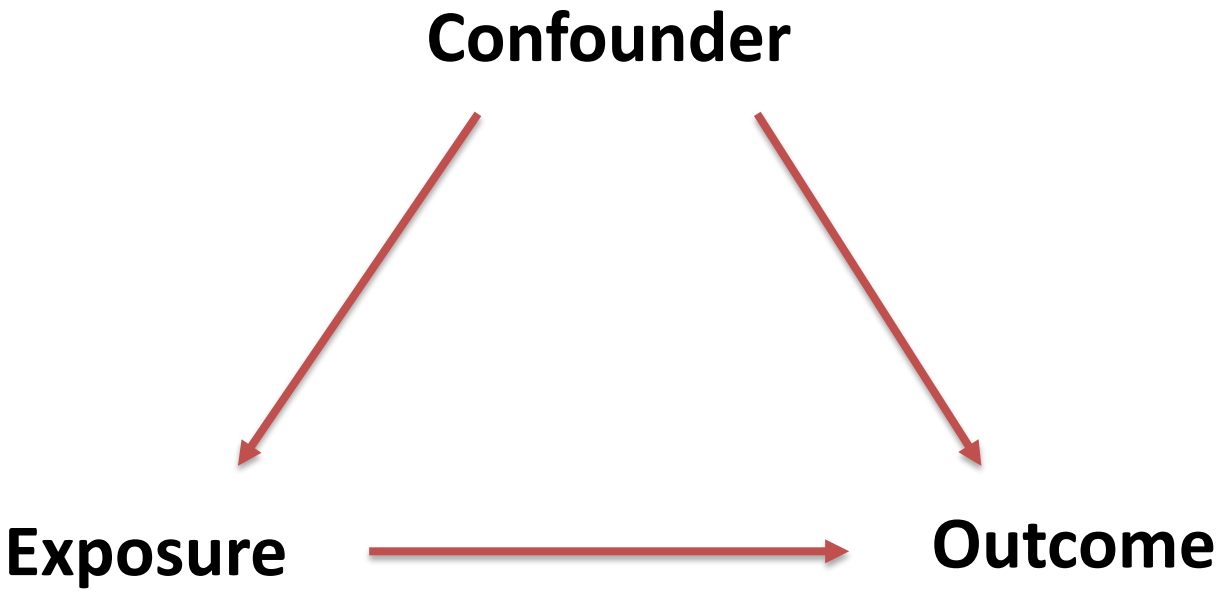
# Class Effect

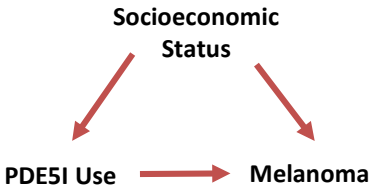
- **Assumes all medications within a class are closely related in chemical structure, pharmacology, therapeutic activity, and adverse reactions**
  - Tadalafil and sildenafil are both PDE5-Inhibitors which are highly specific for PDE5
    - They appear to have similar pharmacologic and therapeutic activity
  - Tadalafil and sildenafil have a similar side-effect/adverse reaction profile overall

# Class Effect

- **In molecular experiments in melanoma cell lines, three PDE5-I have been evaluated together with similar findings**
  - In Arozarena (2011) (JX85), experiments evaluated the effects of sildenafil, tadalafil, and vardenafil on various outcomes:
    - The findings in these cellular experiments are relatively consistent across the three PDE5-I
  - Dhayade (2016) (JX87) in a human melanoma cell line evaluated cGMP levels from exposure to each of these meds
- **Regarding the epidemiologic studies: the authors combine these medications together for their analyses, as a class effect**
  - The most common variable has been a variable of PDE5-I use (e.g. ever use)

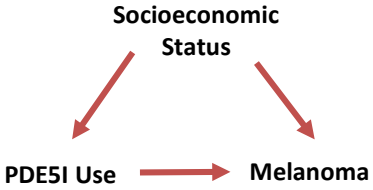
# Confounders






# Socioeconomic Status (SES)

- **No single definition of SES**
- **Data inconclusive whether or not there is an association between SES and PDE5-I use and separately between SES and melanoma**
  - **Therefore SES is not clearly a confounder of this association**
- **Studies considered SES as a potential confounder**
  1) Controlled for SES by study design
     - Veterans (Christie 2019) (PX72)
     - Health Professionals (Li 2014) (JX90)




# Socioeconomic Status (SES)

## 2) Adjusted for SES in analyses

- **Pottegard 2016: Education Level**

Results V). Similarly, supplementary analyses in DNHR showed that educational level, a determinant of health-care utilisation, constituted the most influential covariate in the adjusted analyses reducing the overall OR from 1.28 to 1.24, whereas adjustment for the remaining confounders only reduced the OR from 1.28 to 1.26 (data not shown). The generally marginal confounding was in accordance with the high degree of similarity in characteristics of cases and controls (Table 1).

- **Loeb 2015: Education Level, Annual Income**

Table 4. Odds Ratios of Malignant Melanoma in All Stages by Type of Phosphodiesterase Type 5 Inhibitor

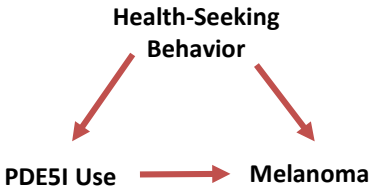
| No. of Filled Drug Prescriptions | No. (%) Cases (n = 4020) | No. (%) Controls (n = 19 972) | Odds Ratio (95% CI) Crude | Odds Ratio (95% CI) Adjusted |
|---|---|---|---|---|
| Sildenafil | | | | |
| None | 3747 (93) | 18 828 (94) | 1 [Reference] | 1 [Reference] |
| 1 | 118 (3) | 482 (2) | 1.23 (1.00-1.51) | 1.17 (0.96-1.44) |
| 2-5 | 98 (2) | 407 (2) | 1.23 (0.98-1.53) | 1.16 (0.92-1.45) |
| ≥6 | 57 (1) | 255 (1) | 1.12 (0.84-1.50) | 1.06 (0.79-1.42) |
| Vardenafil or tadalafil | | | | |
| None | 3811 (95) | 19 164 (95) | 1 [Reference] | 1 [Reference] |
| 1 | 68 (2) | 275 (1) | 1.25 (0.95-1.64) | 1.12 (0.85-1.47) |
| 2-5 | 76 (2) | 307 (2) | 1.24 (0.96-1.60) | 1.11 (0.86-1.44) |
| ≥6 | 65 (2) | 226 (1) | 1.45 (1.10-1.92) | 1.29 (0.97-1.71) |

Adjusted for comorbidity, marital status, educational level, and annual income.

- **Matthews 2016: Smoking Status, Alcohol Use, Deprivation, and BMI**

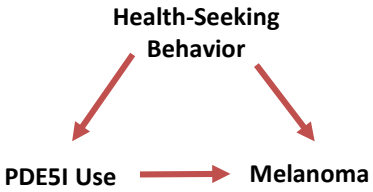
Table 2. Crude rate for malignant melanoma and control outcomes by exposure to PDE5 inhibitors, and unadjusted and adjusted hazard ratios.

| Outcome by Exposure | Number of Events | Person-Years of Follow-Up (100,000s) | Crude Rate (per 100,000 Person-Years) | Unadjusted HR* (95% CI) | Adjusted HR† (95% CI) | *p*-Value |
|---|---|---|---|---|---|---|
| *Primary outcome* | | | | | | |
| Malignant melanoma | | | | | | 0.04 |
| Ever exposed | 321 | 7.4 | 43.7 (39.1, 48.7) | 1.16 (1.03, 1.31) | 1.14 (1.01, 1.29) | |
| Unexposed | 994 | 27.0 | 36.8 (34.5, 39.1) | | | |




# Health-Seeking Behavior (HSB)

- **No precise definition**
- **No data showing that people with health-seeking behavior preferentially use PDE5-I**
  - **Therefore HSB is not clearly a confounder of this association**
- **Studies considered HSB as a potential confounder**
  1) Participant selection
     - Li 2014 – All participants are Health Professionals




# Health-Seeking Behavior (HSB)

## 2) Studies adjusted for HSB

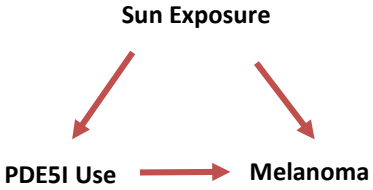
- **Lian 2016: Flu, Colonoscopy, PSA**

(Figure 2 and Supplementary Tables 1–7). Specifically, when restricting the cohort to patients with health-seeking behaviors, the use of PDE5-Is was associated with an increased risk of melanoma skin cancer (HR: 1.46; 95% CI, 1.05–2.04), with evidence of a pattern in terms of prescriptions and pills received (seven or more prescriptions: HR: 1.64 [95% CI, 1.12–2.40]; ≥25 pills: HR: 1.69 [95% CI,

- **Pottegard 2016: Ambulatory Visits**

| Adjusted OR[1] | Adjusted OR[2] | Adjusted OR[3] |
|---|---|---|
| 1.00 (ref.) | 1.00 (ref.) | 1.00 (ref.) |
| 1.17 (1.05–1.30) | 1.13 (1.01–1.27) | 1.08 (0.97–1.22) |
| 1.21 (0.99–1.47) | 1.15 (0.95–1.41) | 1.09 (0.89–1.33) |

OR Differences for Health-Seeking:
Ever Use - 0.05
High Use - 0.06



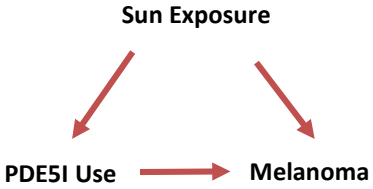

# Sun Exposure

Table 1. Baseline Characteristics of Study Population According to Recent Use of Sildenafil Citrate for Erectile Dysfunction[a]

| Characteristic | Recent Sildenafil Use[b] No (n = 24 470) | Recent Sildenafil Use[b] Yes (n = 1378) | *P* Value[c] |
|---|---|---|---|
| Age, mean (SD), y | 64.8 (8.8) | 66.1 (7.7) | <.001 |
| Body mass index, mean (SD)[d] | 25.6 (5.7) | 26.1 (4.8) | <.001 |
| Physical activity, mean (SD), metabolic equivalent h/wk | 34.1 (40.6) | 33.7 (34.3) | .68 |
| Current smoking | 5.6 | 4.8 | .23 |
| Family history of melanoma | 4.4 | 5.6 | .10 |
| Burn or blistering skin reaction to the sun | 68.7 | 68.3 | .73 |
| UV index of residence ≥7 | | | |
| At birth | 27.6 | 28.3 | .63 |
| At age 15 y | 29.2 | 29.6 | .76 |
| At age 30 y | 34.3 | 36.9 | .07 |
| Natural red or blond hair | 13.2 | 11.9 | .24 |
| ≥6 moles on the arms (≥3-mm diameter) | 4.8 | 4.7 | .82 |
| History of ≥6 severe or blistering sunburns | 35.1 | 38.6 | .01 |
| Sun exposure ≥11 h/wk | | | |
| College/high school age | 50.2 | 50.6 | .77 |
| Age 25-35 y | 32.2 | 28.9 | .03 |
| Age 36-59 y | 27.8 | 24.1 | .01 |
| Age ≥60 y | 27.1 | 24.3 | .05 |
| Erectile dysfunction | 27.1 | 61.5 | <.001 |
| Physical examination | 85.9 | 91.1 | <.001 |
| Recent use of other erectile dysfunction treatment | 0.0 | 7.6 | <.001 |
| Ever use of sildenafil | 1.0 | 100.0 | <.001 |
| Ever use of other erectile dysfunction treatment | 1.0 | 36.6 | <.001 |

- **No evidence sun exposure varies between users and non-users**
- **For some measures, sun exposures higher for non-users**

Li, 2014 (JX90)




# Sun Exposure

- **Not appropriate measure for ultraviolet exposure in melanoma**
  - Melanoma often occurs on intermittently exposed skin
  - BCC, SCC, SK often occurs on chronically exposed

- **Some studies looked at association between PDE5I and BCC or SCC or SK**
  - Findings were mixed
  - Secondary or post-hoc analysis: Studies weren't designed to look at these associations
  - SK → PDE5-I: Don't know that men with SK are the same as those from the primary analysis

# Causal Assessment

- **Bradford-Hill Methodology:**
  - Causal assessment of criteria (9 factors):
    - (1) Strength of association, effect size
    - (2) Consistency or reproducibility
    - (3) Specificity
    - (4) Temporality
    - (5) Biological gradient or dose-response
    - (6) Plausibility
    - (7) Coherence
    - (8) Experiment
    - (9) Analogy
  - Not all criteria need to be met
    - No rank order
  - Widely accepted method for assessing causality

# Causal Assessment

- **(1) Strength of Association, Effect Size:**
  - This criterion states that one factor to consider is how strong the association is between the outcome (melanoma) and exposure (sildenafil and tadalafil).
  - Almost all outcomes are positive, some near or above 2.0, and many are statistically significant, including after adjustment.
    - Weighed highly.

# Causal Assessment

- **(2) Consistency or Reproducibility:**
  - This criterion means that the increased risk, or association, should be seen across different studies, populations, databases and time frames.
  - Positive associations were consistent and reproduced – observed over time, across studies conducted in different populations, in different countries and using varied study designs.
    - Weighed highly.

# Causal Assessment

- **(3) Specificity:**
  - The criterion of specificity means that the effect seen is a specific effect attributed to a specific cause. Because outcomes (cardiovascular disease, for example) can have multiple causes (diabetes, cigarette smoking, diet, etc.), it is often not possible to attribute a single outcome to a single cause. If specificity does exist, it strengthens the causation conclusion, but its absence does not preclude a casual conclusion.
  - Criterion rarely met.
    - Low weight.

# Causal Assessment

- **(4) Temporality:**
  - This criterion states that the effect of interest must occur after the suspected cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay). For example, the event must come after the drug has been ingested.
  - Exposure occurred prior to diagnosis in every study.
    - Weighed highly.

# Causal Assessment

- **(5) Biological Gradient / Dose-Response:**
  - The criterion of dose response means that greater exposure should generally lead to greater incidence of the effect.
  - Evidence of dose-response was seen in some but not all of the reports.
    - With a drug that is used on an as-needed basis, establishing dose-response is not always feasible.
    - In the case of a rare outcome, such as melanoma, studies may be underpowered for sub-group analyses required to evaluate dose-response.
    - Issues with variation in measurement of exposure across the studies could contribute to inconsistencies for dose-response.
      - Weighed moderately.

# Causal Assessment

- **(6) Plausibility:**
  - This criterion means that a biologically plausible mechanism exists between the outcome of interest and the exposure.
  - Plausible biological mechanism of action in published literature.
    - Weighed highly.

# Causal Assessment

- **(7) Coherence:**
  - Coherence between epidemiological and laboratory findings increases the likelihood of an effect, meaning that the data and association being observed should be consistent (or not conflicting with) known facts of the biology and history of the disease.
  - There is a biologic plausibility consistent with the epidemiological findings.
    - Weighed highly.

# Causal Assessment

- **(8) Experiment:**
  - The criterion of experiment contemplates that evidence drawn from experimental manipulation is a compelling factor for causation.
  - Randomized controlled trial not feasible or ethical.
    - Low weight.

# Causal Assessment

- **(9) Analogy:**
  - With analogy, the effect of similar factors may be considered. In other words, the effect of similar drugs and similar outcomes may be considered in support of a causation conclusion.
  - There are several different types of drugs that have been shown to be causally associated with melanoma skin cancer (including diuretics, immunosuppressant drugs, and other photosensitizing drugs).
    - Low weight.

# Conclusion

- **It is my opinion to a reasonable degree of medical certainty that there is a causal association between sildenafil use and the development of melanoma in a vulnerable subset of patients.**

- **It is my opinion to a reasonable degree of medical certainty that there is a causal association between tadalafil use and the development of melanoma in a vulnerable subset of patients.**